protein in yeast to provide the advantages as noted by Chang and Hitzeman of achieving high level expression of beta-amyloid protein directly into media without presequence or other artifacts of expression. This modification provides for the advantages of conducting the aggregation assay either directly in media or without the need for further purification of the peptide and without the further step of cell lysis to obtain pure peptide product. This is additionally advantageous because cell lysis is noted to contaminate recovery with immature product forms. One of skill in the art would have expected positive results using this modification given the suggestion of Cordell to achieve such expression in yeast and the further teachings of Chang and Hitzeman of the advantages of high level expression, processing and secretion of heterologous proteins into yeast media. This modification further provides the ability to test aggregation in such media directly. Alternatively testing may occur following purification of peptide without the further necessity of cell lysis and potential contamination by alternative immature forms of the peptide. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

Applicant respectfully traverses the rejection in view of the following comments.

Independent claim 1 is directed to a method of identifying a candidate substance that inhibits the aggregation of a mammalian aggregate-prone amyloid protein. The claimed method includes the following steps: (a) contacting a yeast cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with a candidate substance under conditions effective to allow aggregated amyloid formation; and (b) determining the ability of the candidate substance to inhibit the aggregation of the aggregate-prone amyloid protein.

Cordell describes methods of screening to identify agents that can reduce preamyloid aggregate formation. However, Cordell does not describe an assay that uses a yeast host cell expressing a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide to evaluate candidate substances for their ability to inhibit the aggregation of the aggregate-prone amyloid protein. It was as a result of this deficiency in Cordell that the Board of Patent Appeals and Interferences, in its Decision dated February 27, 2004, reversed the Examiner's previous rejection under 35 U.S.C. § 102(b) and concluded that Cordell did not anticipate claims 1, 3, 7, 12, 13, 15, 17-19, and 37.

The secondary references (Hitzeman and Chang) cited by the Examiner in the present obviousness rejection do not add what is lacking in Cordell. Hitzeman describes transformation of yeast with an expression vector encoding a polypeptide containing a signal sequence and a heterologous protein, such that the signal sequence results in secretion of the heterologous protein from the yeast. Chang also describes methods of secreting a heterologous protein from yeast. Consistent with the preceding comments, the Examiner stated that both Hitzeman and Chang "teach expression, processing and secretion of heterologous protein by yeast." Office Action at page 4. As detailed in the block quote reproduced above from the Office Action, the Examiner asserted that one of skill in the art would "be motivated by Chang and Hitzeman to modify the screening assay of Cordell so as to express the mammalian aggregate-prone protein in yeast to provide the advantages as noted by Chang and Hitzeman of achieving high level expression of beta-amyloid protein directly into media."

A determination of obviousness under 35 U.S.C. §103 (a) based on a combination of references requires that the combination as suggested or motivated by the art must yield the claimed invention. In re Dow Chemicals Co., 837 F.2d 469, 472-73 (Fed. Cir. 1988).

Applicant does not agree with the Examiner's assertion that the person of ordinary skill in the art at the time the present application was filed would have had the requisite suggestion or motivation to combine Cordell with Hitzeman and Chang. Nonetheless, even if the combination suggested by the Examiner were to be made, such combination would clearly not result in the claimed invention. As acknowledged by the Examiner throughout the Office Action, Hitzeman and Chang describe the secretion of proteins by yeast. It was for this reason that the Examiner concluded that the combination of the cited references would result in an assay conducted on a protein secreted from yeast into cell culture media.

In contrast to the method resulting from the Examiner's proposed combination of references, claim 1 requires that the method be carried out in a yeast cell (i.e., not using a secreted protein) under conditions effective to allow aggregated amyloid formation of the chimeric aggregate-prone amyloid protein. It is under these conditions that, according to claim 1, a candidate substance is evaluated for it ability to inhibit the aggregation of the

aggregate-prone amyloid protein in the yeast cell. Because the method that results from the Examiner's suggested combination of references entails the use of a secreted or purified protein, and is not carried out in a yeast cell as is required by claim 1, the combination of the cited references necessarily fails to suggest the method of claim 1.

In light of these comments, applicant respectfully submits that the combination of Cordell, Hitzeman, and Chang does not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection of independent claim 1 and dependent claims 3, 7, 9, 12, 13, 15, 17-19, and 37.

On pages 5-6 of the Office Action, the Examiner rejected dependent claims 8, 17, 18, and 20 as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Chalfie et al. (1994) Science 263:802-05 ("Chalfie").

The Examiner cited Chalfie as allegedly describing the use of green fluorescent protein as a marker for gene expression and asserted that the skilled artisan would have been motivated to use green fluorescent protein to monitor protein aggregation in yeast cell culture media.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Examiner would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Chalfie provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 8, 17, 18, and 20 should also be in condition for allowance.

On pages 6-8 of the Office Action, the Examiner rejected dependent claims 7, 10, and 11 as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Tikhonenko et al. (1995) Oncogene 11:1499-508 ("Tikhonenko").

The Examiner cited Tikhonenko as allegedly describing the use of the glucocorticoid receptor element as a marker for protein inducible expression and asserted that the skilled artisan

would have been motivated to modify the fusion proteins of Cordell to use the glucocorticoid receptor to monitor and induce protein expression in a cell culture assay.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Examiner would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Tikhonenko provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 7, 10, and 11 should also be in condition for allowance.

On pages 8-9 of the Office Action, the Examiner rejected dependent claim 16 as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Nordstedt et al. (1994) J. Biol. Chem. 49:30773-76 ("Nordstedt").

The Examiner cited Nordstedt as allegedly teaching that the Abeta peptide develops protease resistance in association with its polymerization into amyloid fibrils. The Examiner asserted that the skilled artisan would have been motivated to modify the methods of Cordell to determine the ability of a candidate substance to inhibit aggregation by assessing the aggregate-prone amyloid protein aggregation as detected by increased protease resistance.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Examiner would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Nordstedt provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claim 16 should also be in condition for allowance.

On pages 9-11 of the Office Action, the Examiner rejected dependent claims 14 and 22 as allegedly unpatentable over Cordell, Hitzeman, and Chang as set forth above and further in view of Patino et al. (1996) Science 273:622-26 ("Patino").

The Examiner cited Patino as allegedly describing Sup35 as a yeast homologue of prion protein and Hsp104 overexpression in yeast cells as capable of converting Sup35 from an aggregating form to a non-aggregating form.

As detailed above, the combination of Cordell, Hitzeman, and Chang suggested by the Examiner would result in an assay conducted on a protein secreted into cell culture media, rather than an assay carried out in a yeast cell as is required by claim 1. Patino provides nothing that supplements the deficiencies of Cordell, Hitzeman, and Chang or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, dependent claims 14 and 22 should also be in condition for allowance.

CONCLUSIONS

Applicant submits that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Three Month Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 17481-004001.

Respectfully submitted,

Date: October 20, 2004

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